

# Fib

Repeated pain signals in the periphery may sensitize spinal cord neurons, resulting in amplified and prolonged signals traveling to the brain

# fibromyalgia

## Psychiatric drugs target CNS-linked symptoms

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**P**atients with fibromyalgia are a heterogeneous group, yet many describe a common experience: seeing multiple physicians who seem unable or unwilling to provide a diagnosis or treat their symptoms. This situation may be changing with the recent FDA approval of an anticonvulsant and 2 antidepressants for managing fibromyalgia symptoms.

These medications—pregabalin, duloxetine, and milnacipran—reflect a revised understanding of fibromyalgia as a CNS condition, rather than an inflammatory process in the muscles or connective tissue. As a result, psychiatrists—because of our experience with CNS phenomena and managing antidepressant and anticonvulsant medications—are likely to play a larger role in treating fibromyalgia.

### CASE REPORT

#### 'Just too tired'

Ms. D, age 50, has a history of migraine headaches and is referred by her primary physician for evaluation of depression and anxiety. She reports deteriorating mood over 6 months, beginning when a minor car accident left her "very sore the next day."

"Nothing helps" the persistent pain in her back, shoulders, and thighs, which she rates as 7 to 8 on a 0-to-10 pain scale. She describes an intense ache, "like having the flu," that worsens with activity and in stressful situations. She also experiences nausea and intermittent diarrhea, debilitating fatigue, and sleep disturbance.

continued



## Fibromyalgia

### Clinical Point

Musculoskeletal pain is not the most problematic symptom for many patients with fibromyalgia

**Table 1**

### Medical and cognitive symptoms related to fibromyalgia

<b>Neurologic</b>	Tension/migraine headache
<b>Psychiatric</b>	Memory and cognitive difficulties Mood disturbance Anxiety disorders
<b>Ear, nose, throat</b>	Sicca symptoms Vasomotor rhinitis Vestibular complaints
<b>Cardiovascular</b>	Neurally mediated hypotension Mitral valve prolapse Noncardiac chest pain
<b>Gastrointestinal</b>	Esophageal dysmotility Irritable bowel syndrome
<b>Urological</b>	Interstitial cystitis
<b>Gynecological</b>	Vulvodynia Chronic pelvic pain
<b>Oral/dental</b>	Temporomandibular joint syndrome
<b>Other (general)</b>	Chronic fatigue syndrome Sleep disturbances Idiopathic low back pain Multiple chemical sensitivity

**Table 2**

### Fibromyalgia: Structured interview for diagnosis

**A.** Generalized pain affecting the axial, plus upper and lower segments, plus left and rights sides of the body

**Either B or C:**

**B.** At least 11 of 18 reproducible tender points

**C.** At least 4 of the following symptoms:

- Generalized fatigue
- Headaches
- Sleep disturbance
- Neuropsychiatric complaints
- Numbness, tingling sensations
- Irritable bowel symptoms

**D.** It cannot be established that disturbance was due to another systematic condition

Source: Reference 4

Ms. D reports she is depressed because she feels “just too tired” after work to keep up with social activities or housework. Her physician’s referral notes a normal physical exam except for tenderness over her upper back and hips. Laboratory testing is negative.

### Making the diagnosis

American College of Rheumatology (ACR) criteria for fibromyalgia require widespread pain for at least 3 months. “Widespread” is defined as pain in the axial skeleton, left and right sides of the body, and above and below the waist. Pain must be found in at least 11 of 18 tender point sites on digital palpation using a force of approximately 4 kg/cm<sup>2</sup>.<sup>1</sup> For many fibromyalgia patients, however, musculoskeletal pain is not their most problematic symptom (*Table 1*). They may suffer:

- migraine and tension headaches (10% to 80% of patients)
- irritable bowel syndrome (32% to 80%)<sup>2</sup>
- mood disorders (major depressive disorder [62%], bipolar disorder [11%])
- anxiety disorders (panic disorder [29%], posttraumatic stress disorder [21%], social phobia [19%]).<sup>3</sup>

ACR criteria are useful in research but lack many common symptoms and comorbidities. A structured interview that follows the DSM-IV-TR format incorporates other symptoms into the diagnosis (*Table 2*).<sup>4</sup>

Because patients with fibromyalgia often meet criteria for somatization or somatoform disorders, how to classify them—as medically or psychiatrically ill—is controversial. Some patients believe their mood or anxiety problem stems from the difficulty they experience dealing with their physical symptoms, and if they could feel better physically they would not be depressed or anxious. Others believe their psychiatric symptoms impede their ability to help themselves feel better.

Consider fibromyalgia in any patient with widespread pain of unknown cause. Before making the diagnosis, rule out other illnesses that present with similar symptoms (*Table 3*). Because many patients newly diagnosed with fibromyalgia worry

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Download a form for patients to report fibromyalgia symptoms. Saves time, structures office visits.

[CurrentPsychiatry.com](http://CurrentPsychiatry.com)

Table 3

## Differentiating fibromyalgia from illnesses with similar symptoms

Illness	Tests to differentiate from primary fibromyalgia
<b>Rheumatic diseases</b>	
Osteoarthritis	Radiographs
Spondyloarthropathies, rheumatoid arthritis	Rheumatic markers (antinuclear antibody, rheumatoid factor, antibodies)
Systemic lupus erythematosus, polymyalgia rheumatica	Inflammatory markers (ESR, C-reactive protein)
Osteomalacia	Vitamin D level
Myopathy	CPK
<b>Neurologic</b>	
Multiple sclerosis, Chiari's malformation, spinal stenosis, radiculopathy	MRI
Neuropathy	EMG
<b>Endocrine</b>	
Hypothyroidism	TSH
Diabetes	Basic chemistry panel with fasting glucose
<b>Other</b>	
<b>Infectious</b>	
Lyme disease	CBC Lyme titer
Hepatitis	Hepatitis antibody panel, liver function tests
Anemia	Hemoglobin/hematocrit
Cancers	Routine cancer screening tests, bone scan, blood chemistries specific for suspected primary cancer

ESR: erythrocyte sedimentation rate; CPK: creatine phosphokinase; EMG: electromyography; TSH: thyroid-stimulating hormone; CBC: complete blood count

### Clinical Point

Fibromyalgia patients show lower levels of serotonin, norepinephrine, and dopamine metabolites in cerebrospinal fluid

that something “more serious” may be going on, confirm the diagnosis with appropriate testing and physical examination, usually by a rheumatologist or primary care physician.

#### CASE CONTINUED

#### Central pain sensitization

As you elicit more details about Ms. D's mood, she continues to focus on her physical symptoms. She states that some days she wishes to die because her pain gets so bad, but she denies any plan or intent to harm herself. She worries that her symptoms will worsen and that she will become completely disabled.

Her primary physician attempted to relieve Ms. D's pain with multiple trials of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclobenzaprine. She says she gained no benefit from the NSAIDs and discontinued the muscle relaxant because it made her too sleepy.

Fibromyalgia affects 3.5% of women and 0.5% of men.<sup>5</sup> It runs in families with histories of fibromyalgia and major mood and anxiety disorders, suggesting genetic links.<sup>6</sup> Defects in genes controlling serotonin and norepinephrine have been implicated.<sup>7-9</sup>

Fibromyalgia patients show lower levels of serotonin, norepinephrine, and dopamine metabolites in cerebrospinal fluid (CSF), compared with controls.<sup>10</sup> These neurotransmitters may inhibit descending pain pathways in the CNS, and low levels in the brain and spinal cord may inhibit CNS regulation of pain impulses from the periphery.<sup>11</sup>

Although many patients describe muscle pain, evidence suggests central pain augmentation rather than an abnormality of muscle or connective tissue.<sup>12</sup> Some studies have found evidence of “windup,” in



## Fibromyalgia

### Clinical Point

Many patients expect to resume an energetic, pain-free life, which usually is not the case with fibromyalgia

#### Box

## Managing unrealistic expectations of fibromyalgia patients

**BELIEF:** 'A magic pill exists that will resolve all my symptoms and have no side effects'

**Clinical evidence:** Most medications that have been studied were effective in 30% to 50% of patients and reduced pain scores by 30% to 50%.

**Patient education:** Explain to the patient with a pain rating of 7 at the first visit that achieving a pain level of 3 to 4 may be possible with treatment. Even with successful treatment, symptoms may flare intermittently. As with any treatment, adverse effects may occur. Discuss these, so the patient is not surprised.

**BELIEF:** 'I can't exercise'

**Clinical evidence:** Most patients experience more fatigue and pain with physical activity, but exercise is important to maintain physical function.

**Patient education:** When discussing an exercise program, focus on what the patient can do. Most patients attempt too much, too soon; advise them to start at a tolerable level (such as 2 to 3 minutes of aerobic activity daily for the first week) and gradually increase as tolerated.

**BELIEF:** 'You (the psychiatrist) can make me feel better'

**Clinical evidence:** Psychiatrists can help by prescribing appropriate medications, but much of the burden falls on the patient to maintain a healthy, active lifestyle and to manage stressors in an adaptive manner.

**Patient education:** A fibromyalgia patient may find relief with a medication, but symptoms may flare if they 'overdo' and take on too many physical or emotional stressors. A consistent, healthy routine is ideal.

**BELIEF:** 'I will eventually become disabled by fibromyalgia'

**Clinical evidence:** Despite little long-term research on fibromyalgia patients, most evidence points to a chronic, fluctuating syndrome that does not worsen with age. Factors that may worsen symptoms include uncontrolled comorbid conditions, chronic opiate use, inactivity, and deconditioning.

**Patient education:** Discourage long-term physical disability; exercise and maintaining an active daily routine helps patients avoid focusing in a nonadaptive manner on their dysfunction and symptoms.

Source: Sharon B. (Shay) Stanford, MD

which second-order neurons in the spinal cord become sensitized by repeated signals from first-order neurons in the periphery, resulting in amplified and prolonged pain signals traveling to the brain.<sup>13</sup>

Levels of substance P—a primary transmitter of pain impulses—are significantly higher in CSF of fibromyalgia patients compared with controls.<sup>14</sup> This finding, in addition to low levels of serotonin and norepinephrine, indicates that pain signals are ascending unchecked to be processed by the brain.

Neuroimaging studies confirm this observation. In a study using functional magnetic resonance imaging (fMRI), researchers applied pressure to the thumbnails of fibromyalgia patients and controls until each subject reported pain:

- Twice as much pressure was required before controls rated their pain at a level similar to that of fibromyalgia patients.
- When controls and fibromyalgia patients reported similar pain, a very high

degree of overlap was seen in brain areas responsible for pain processing. This indicates that fibromyalgia patients and controls were experiencing the pain they reported in the same way.<sup>15</sup>

### Treating the whole patient

As a clinician who specializes in fibromyalgia, I counteract my patients' and my own frustration with this condition by structuring office visits, determining realistic treatment goals, and treating all symptoms as part of a common syndrome rather than individual illnesses.

**Structure office visits.** Before every visit, have patients rate each symptom domain and write their top 2 or 3 concerns for that day (for a sample form, see this article at [CurrentPsychiatry.com](http://CurrentPsychiatry.com)). Focusing on the patient's most troublesome symptoms can help both of you feel greater satisfaction with treatment.

**Educate patients.** Ask them to discuss their beliefs about fibromyalgia; many know others with this condition or have researched diagnosis and treatment. Before developing a treatment plan, explain that their symptoms are chronic and all part of the same syndrome. Describe their pain as a complex phenomenon with possible peripheral and CNS components. Guide them to reputable Web sites and resources (see *Related Resources*, page 50).

**Set realistic expectations.** Many patients expect to resume an energetic and pain-free life, which usually is not the case with fibromyalgia (*Box*). Most medications are considered successful if they reduce pain by 30% to 50%, and side effects can be problematic. Discuss side effects before treatment begins to reduce patients' anxiety and improve compliance in the first weeks.

**Cognitive-behavioral therapy (CBT)** for fibromyalgia incorporates relaxation techniques, helping patients view symptoms as manageable, reinforcing adaptive coping skills, and teaching them how to monitor thoughts, feelings, and behavior to change the view that they are helpless victims. A modest course of 6 weekly group CBT sessions significantly improved physical functioning in 25% of fibromyalgia patients (n=76) compared with 12% in a standard-care group (n=69), even though patients' pain severity did not improve.<sup>16</sup>

**Recommend exercise, lifestyle changes.** Aerobic exercise can significantly improve well-being and physical functioning in fibromyalgia patients.<sup>17</sup> Low-impact aerobics, such as done in warm water, usually are well tolerated, although any low-impact exercise can help. Because fibromyalgia symptoms often increase with physical activity, counsel patients to begin with a few minutes daily and increase very slowly each week.

Lifestyle changes are as important as medications in controlling fibromyalgia symptoms. In addition to exercise, recommend that patients:

- follow a daily routine
- pace activity to avoid exacerbating symptoms
- reduce stress.

Sometimes, I use the analogy of diabetes: treating fibromyalgia with medication but



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## Fibromyalgia

### Clinical Point

Pregabalin may be a beneficial first choice for patients who report pain and sleep as major issues

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Details of clinical trials that supported fibromyalgia indications for 3 CNS medications. [CurrentPsychiatry.com](http://CurrentPsychiatry.com)

Table 4

## Off-label medications shown to benefit patients with fibromyalgia

Drug	Comment
<b>Amitriptyline</b> <sup>27,28</sup>	Considered first-line because of studies supporting its use, low cost, and wide availability; may be associated with more side effects than newer medications
<b>Gabapentin</b> <sup>29</sup>	Possible alternative to pregabalin but may not be as well tolerated
<b>Tramadol</b> <sup>30</sup>	May help with breakthrough pain; use with extreme caution in patients taking antidepressants because of serotonin syndrome risk
<b>Fluoxetine</b> <sup>31</sup>	Dosages of 40 to 60 mg/d may help patients who do not tolerate SNRIs
<b>Venlafaxine</b> <sup>32</sup>	Dosages of 150 to 225 mg/d may be an alternative to other SNRIs

SNRIs: serotonin/norepinephrine reuptake inhibitors

without changing lifestyle is like prescribing medication for a diabetic patient without changing diet. Follow up on this “homework” at each visit to reinforce that patients helping themselves is an important part of treatment.

### New direction with medications

**Pregabalin** is an anticonvulsant that binds to the alpha-2-delta subunits of neurons’ voltage-gated calcium channels. This activity reduces calcium influx at nerve terminals and inhibits release of excitatory neurotransmitters, such as substance P and glutamate.<sup>18</sup> In June 2007, pregabalin was the first medication FDA-approved for fibromyalgia.

Two placebo-controlled trials<sup>19,20</sup> showed that pregabalin at 150 mg bid, 225 mg bid, or 300 mg bid significantly reduced weekly mean pain scores in fibromyalgia patients. For details of these trials, see this article at [CurrentPsychiatry.com](http://CurrentPsychiatry.com). The most common side effects—dizziness, somnolence, peripheral edema, blurred vision, and weight gain—were regarded as mild to moderate in 87% of patients.<sup>21</sup>

Although a dosage of 300 mg bid also was studied, the FDA approved pregabalin at dosages of 150 mg bid and 225 mg bid for fibromyalgia.<sup>22</sup>

**Duloxetine** is a serotonin/norepinephrine reuptake inhibitor (SNRI) thought to inhibit dorsal horn neurons’ response to peripheral pain signals by increasing serotonin and norepinephrine in the

brain and spinal cord. This SNRI was first FDA-approved for diabetic peripheral neuropathic pain and major depressive disorder. Approval for fibromyalgia at 60 mg/d in June 2008 was based on 2 placebo-controlled, double-blind, 12-week trials comprising 874 patients.<sup>23,24</sup> For detailed findings of these studies and a 6-month fixed-dose trial,<sup>25</sup> see this article at [CurrentPsychiatry.com](http://CurrentPsychiatry.com).

In clinical trials, duloxetine dosages of 60 mg/d and 120 mg/d were significantly more effective than placebo. The most common side effects were nausea, constipation, excessive sweating, and somnolence.<sup>23-25</sup>

**Milnacipran** is an SNRI that was approved for treating fibromyalgia in January 2009 at dosages of 50 mg bid and 100 mg bid. Like other SNRIs, milnacipran is thought to work by inhibiting pain signals through increasing serotonin and norepinephrine in the brain and spinal cord. Milnacipran has a higher selectivity for norepinephrine reuptake compared with duloxetine, which may mean these medications will have different effects in different patients. Although milnacipran is approved as an antidepressant in other countries, the FDA has not approved it for treating depression in the United States.

For details of a 15-week, double-blind, placebo-controlled trial of milnacipran in patients with fibromyalgia, see this article at [CurrentPsychiatry.com](http://CurrentPsychiatry.com). Side effects in clinical trials were similar to those of duloxetine, with nausea, constipation, and increased sweating being most prominent.<sup>26</sup>

**Other medications**, such as the first-line agent amitriptyline, have shown beneficial effects in fibromyalgia but are not FDA-approved for this indication (*Table 4*).<sup>27-32</sup>

**Choosing medications.** When prescribing one of the FDA-approved medications to treat fibromyalgia, consider their benefits and side effects.

Pregabalin may be a beneficial first choice for patients who report pain and sleep as major issues. Although the medication's label recommends starting with twice-daily dosing, patients might better tolerate an initial dose of 50 to 75 mg in the evening, with the morning dose added later. Pregabalin can be useful in patients taking multiple medications because of its renal clearance, resulting in low risk of interactions with drugs metabolized by liver enzymes. It also can be useful in patients who have not tolerated antidepressants in the past or in whom antidepressants are contraindicated.

If a patient has a history of depression or discontinuing medications because of sedating side effects, an antidepressant such as duloxetine or milnacipran may be more successful than starting with pregabalin. In general, if a patient does not respond to one of these SNRIs, moving on to the other might help. Milnacipran's more selective effect on norepinephrine could be beneficial for some patients, especially those with excessive fatigue. Others, especially those with a high level of anxiety, might respond better to a more balanced SNRI such as duloxetine.

#### CASE CONTINUED

#### Not as hopeless

Ms. D's primary care physician confirms your presumptive diagnosis of fibromyalgia. He prescribes a trial of amitriptyline, which she does not tolerate well because of sedation and weight gain. At her next psychiatric visit, she tells you she remains very frustrated about her physical symptoms and reports that her doctor "has given up on me."

You discuss what a fibromyalgia diagnosis means to her and educate her about the syndrome. You refer her to a colleague who does CBT with chronic pain patients and start her on a low dose of duloxetine (30 mg once daily) to minimize side effects. You discuss possible side effects and that she may need a higher dose to notice improvement in her pain. She seems receptive to starting a graded exercise program, and you encourage her to reduce physical and emotional stress in her life.

When she returns, she reports her pain is somewhat improved and medication side effects have subsided. She is not as hopeless and tells you she is up to 10 minutes of walking daily. You increase duloxetine to 60 mg/d and reinforce her ability to exercise and manage her stress.

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#### Clinical Point

**Milnacipran's more selective effect on norepinephrine could be beneficial for patients with excessive fatigue**

## Bottom Line

Consider fibromyalgia in patients with pain, depression, sleep problems, fatigue, and cognitive dysfunction beyond what is expected for a primary mood disorder. Two antidepressants and an anticonvulsant that target the CNS are FDA-approved for fibromyalgia, although other medications may help. Encourage patients to share in symptom management by exercising and making lifestyle changes. Cognitive/behavioral techniques can help patients manage frustration and hopelessness.





## Fibromyalgia

### Clinical Point

Other patients may respond better to a more balanced SNRI such as duloxetine, especially those with high levels of anxiety

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## Related Resources

- Arthritis Foundation. Fibromyalgia. [www.arthritis.org/disease-center.php?disease\\_id=10](http://www.arthritis.org/disease-center.php?disease_id=10).
- National Fibromyalgia Association. [www.fmaware.org](http://www.fmaware.org).
- Self-management program for patients with fibromyalgia, cosponsored by the National Fibromyalgia Association and Eli Lilly and Company. [www.knowfibro.com](http://www.knowfibro.com).

### Drug Brand Names

Amitriptyline • Elavil, Endep	Milnacipran • Savella
Cyclobenzaprine • Flexeril	Pregabalin • Lyrica
Duloxetine • Cymbalta	Tramadol • Ultram, Ultracet
Fluoxetine • Prozac	Venlafaxine • Effexor, Effexor XR
Gabapentin • Neurontin	

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